Non-invasive assessment of the effect of cardiac sympathetic innervation on metabolism of the human heart

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Abstract. The role of cardiac sympathetic nerves in the regulation of myocardial metabolism is not well defined. Owing to the presence of incomplete reinnervation, heart transplant recipients provide a unique model to study the effects of efferent sympathetic innervation. Using this model, we sought to determine the influence of cardiac sympathetic signals on substrate utilisation and overall oxidative metabolism. In 21 transplant recipients, positron emission tomography was applied to determine sympathetic innervation with the noradrenaline analogue carbon-11 hydroxyephedrine, oxidative metabolism with carbon-11 acetate (n=14), and glucose utilisation with fluorine-18 fluorodeoxyglucose (n=7). The reinnervated area comprised 22%±20% of the left ventricle. Oxidative metabolism was similar in denervated and reinnervated myocardium [0.06±0.01 vs 0.06±0.01/min for k(mono)], while glucose uptake was significantly higher in denervated myocardium (6.9±6.6 vs 6.0±6.2 µmol/min/100 g; P=0.03). Reinnervation mainly occurred in the territory of the left anterior descending artery, where retention of ^{11}C-hydroxyephedrine (6.8±2.7%/min) was higher compared with territories of the left circumflex (4.1±1.7%/min; P<0.01) and right coronary (3.8±1.1%/min; P<0.01) arteries. Oxidative metabolism was similar in all three territories, but compared with the reinnervated territory of the left anterior descending artery (53%±16% of maximum), relative FDG uptake was higher in territories of the left circumflex (76%±6%, P<0.01) and right coronary (67%±10%, P<0.05) arteries. Similar degrees of regional heterogeneity were not observed in normals. Thus, while overall energy production through oxidative metabolism remains unaffected, cardiac utilisation of glucose in the fasting state is increased in the absence of catecholamine uptake sites. Innervated myocardium, however, may preferentially utilise free fatty acids, suggesting a role for sympathetic tone in substrate utilisation.

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Introduction

The preferential substrate utilisation for myocardial energy production is determined by various intracellular and extracellular factors, e.g. plasma substrate levels, concentration of hormones, cardiac workload and tissue oxygenation [1]. The tone of the sympathetic nervous system may also play a role in the modulation of metabolism. Effects on myocardium may be exerted via circulating catecholamines, or via direct cardiac innervation by efferent sympathetic neurons. Circulating catecholamines have been shown to directly stimulate cardiac glucose uptake and glycogenolysis [2], exert inotropic and chronotropic effects which increase oxygen consumption [3, 4], and influence metabolism indirectly by systemic circulatory and metabolic effects [5, 6]. Little, however, is known about the role of cardiac innervation in the regulation of regional metabolism. Some animal models have suggested an effect of autonomic denervation on substrate oxidation [7, 8]. In humans, however, information about the relationship between efferent innervation and metabolism of the heart remains scarce.

The transplanted heart represents a unique model with which to study effects of innervation on human myocardium. Heart transplantation results in initial complete denervation owing to surgical interruption of post-ganglionic sympathetic fibres and rapid depletion of noradrenaline within nerve terminals [9]. Subsequently, sympathetic reinnervation does occur, but remains regionally limited [10, 11, 12]. Owing to this heterogeneity, an intra-individual comparison of metab-

olism in denervated and reinnervated areas of the same heart is possible.

Positron emission tomography (PET) in combination with the catecholamine analogue carbon-11 hydroxyephedrine (HED) can be used for non-invasive detection of sympathetically innervated areas of transplanted hearts [10, 12]. Additionally, PET provides an opportunity to obtain insights into myocardial metabolism: Turnover kinetics of ^{11}C-labelled acetate can be used to determine overall oxidative metabolism [13]. Furthermore, transport and phosphorylation as early steps of glucose metabolism can be assessed by fluorine-18 labelled fluorodeoxyglucose (FDG) [14].

The purpose of this study was to investigate the effect of sympathetic innervation on the metabolism of the human heart. Using non-invasive PET imaging late after transplantation, detection of cardiac presynaptic catecholamine uptake sites was combined with an assessment of regional oxygen consumption or utilisation of glucose, and metabolism in innervated and denervated myocardial areas was compared.

Materials and methods

Patients and study design. We studied 21 heart transplant recipients (19 men, 2 women; mean age 55±7 years) at 6.8±3.8 years after surgery. Transplantation was performed to treat idiopathic dilated cardiomyopathy in 16, and ischaemic cardiomyopathy in five individuals. Between transplantation and inclusion in the study, patients had an average of 2 rejection episodes (range 0–5). At the time of PET imaging, however, all patients were symptom-free, and none showed signs of acute graft rejection as documented by endomyocardial biopsy. Additionally, no patient had angiographic evidence of significant graft vessel disease. Global ventricular function, determined by left ventriculography or echocardiography, was normal. No regional wall motion abnormalities were found.

None of the patients had diabetes mellitus or were receiving medication known to interfere with presynaptic sympathetic innervation. Immunosuppression with cyclosporine A was continued on the day of PET imaging, but all other medication was discontinued for at least 24 h.

All transplant recipients underwent PET with ^{11}C-HED to assess cardiac catecholamine uptake sites. In the same PET session, metabolic imaging was performed: Oxidative metabolism was determined by ^{11}C-acetate in 14 patients (group A). In the remaining seven patients (group B), myocardial glucose uptake was measured by FDG. Both groups were matched for patient age (54±7 years for group A vs 58±4 years for group B; P=0.17), and time between transplantation and PET (6.5±3.5 vs 7.5±4.5 years; P=0.56).

Twenty-six individuals (age 45±14 years; 12 men, 14 women) without clinical and electrocardiographic evidence of heart disease served as control groups for ^{11}C-HED (n=8), ^{11}C-acetate (n=11) and ^{18}F-FDG (n=7). These individuals were used to describe regional patterns of cardiac sympathetic innervation and metabolism in healthy normals.

The study protocol was approved by the ethical committee of the Technische Universität München. Prior to inclusion, all patients gave written informed consent.

Positron emission tomography. Subjects were studied after overnight fasting to achieve constant metabolic conditions for dynamic PET imaging.

An 11-MeV cyclotron (Siemens/CTI, Knoxville, Tenn.) was used for radioisotope production. Radiopharmaceuticals were synthesised as previously described [15, 16, 17]. Imaging was performed using an ECAT 951 or ECAT EXACT whole-body PET scanner (Siemens/CTI, Knoxville, Tenn.).

In all subjects, the imaging procedure started with a transmission scan of 15 min to correct for photon attenuation by tissue. Subsequently, dynamic emission scans were performed after intravenous administration of positron-emitting tracers.

In transplants of group A, myocardial oxidative metabolism was measured first using 300–500 MBq of ^{11}C-acetate and a dynamic image acquisition of 21 frames over 30 min (10×10, 1×60, 5×100, 3×180, 2×300 s). After a break of 50 min to allow for decay of ^{11}C, cardiac sympathetic innervation was assessed by a bolus of 500–700 MBq of ^{11}C-HED and another dynamic imaging sequence of 14 frames over 40 min (6×30, 2×60, 2×150, 2×300, 2×600 s).

In transplants of group B, sympathetic innervation was measured first due to the shorter half-life of ^{11}C as compared with ^{18}F (20 vs 110 min). Then, following a break of 50 min, myocardial glucose utilisation was determined using 300–400 MBq of ^{18}F-FDG and a dynamic sequence of 12 frames over 60 min (12×300 s).

In normals, a single tracer study with either ^{11}C-HED, ^{11}C-acetate or ^{18}F-FDG was performed.

Data analysis. Attenuation-corrected transaxial images were reconstructed by filtered back-projection. For each dynamic image set, a volumetric sampling tool was then applied to a single time frame to create polar maps of static myocardial activity distribution [18]. Myocardial sectors defined by this polar map were transferred to the whole dynamic imaging sequence, and time-activity curves were obtained. Additionally, the arterial input function was derived from a small circular region of interest in the left ventricular cavity.

Global and regional catecholamine uptake sites were quantified by retention of ^{11}C-HED, defined as activity at 40 min after injection divided by the integral of the input function [12].

For ^{11}C-acetate, the early phase of tracer washout was fitted mono-exponentially to obtain the constant k(mono) as a previously validated measure of cardiac oxidative metabolism [19].

Because the initial extraction of ^{11}C-acetate is high, early static images provide an index of regional myocardial perfusion [20]. Thus, polar maps of acetate uptake at 2–3 min after injection were generated additionally for qualitative assessment of perfusion.

From dynamic FDG data, the myocardial metabolic rate of glucose (MMRGlc) was calculated using Patlak graphical analysis and a lumped constant of 0.67 [14].

HED retention, perfusion, k(mono) and MMRGlc were subjected to further regional analysis (Fig. 1): Based on results in denervated hearts, a threshold for HED retention of 7%/min was chosen to distinguish between reinnervated and denervated myocardium in transplant recipients [10]. Regions of interest for denervated and innervated areas were defined for each patient, and transferred to identical positions in corresponding polar maps for k(mono) (group A) or MMRGlc (group B) for intra-individual comparison of myocardial metabolism.

For regional comparison between transplants and normals, polar maps for k(mono), perfusion and MMRGlc were first normalised to their maximum to correct for inter-individual variability. Standardised regions of interest encompassing vascular territories

of the left anterior descending artery (LAD), left circumflex artery (LCX) and right coronary artery (RCA) were then applied, and values expressed as percent of the individual left ventricular maximum were compared. Finally, a non-LAD/LAD index for MMRGlc was calculated by [MMRGlc(LCX/RCA) - MMRGlc(LAD)] / MMRGlc(LCX/RCA), where MMRGlc(LCX/RCA) is the mean FDG uptake of the LCX and RCA territories and MMRGlc(LAD) is the value for the LAD territory.

Statistical analysis. Data are expressed as mean ± standard deviation. Correlation between continuous variables was described by Pearson's correlation coefficient and tested for significance by Fisher's *r* to *z* transformation. A two-tailed paired Student's *t* test was applied for intra-individual comparison of metabolism in innervated and denervated myocardium. Differences between transplant patients and normals were compared using a two-tailed unpaired *t* test. For comparison of parameters in three vascular territories, factorial analysis of variances combined with the Bonferroni-corrected post-hoc *t* test, was applied. A *P* value <0.05 was considered statistically significant except in the case of the post-hoc *t* test according to Bonferroni, where *P* values <0.0167 were considered significant, although *P* values <0.05 were also reported as they were considered to show a trend towards significance.

Results

Presynaptic sympathetic innervation

In heart transplant recipients, 21.7%±19.8% of the left ventricle was reinnervated. The innervated area ranged from 0% to 66% of the ventricle, and was significantly correlated with time after transplantation (r=0.47; P=0.03). In two patients (one in group A, one in group B), maximal HED retention did not reach the threshold of 7%/min, indicating complete denervation.

Reappearance of catecholamine uptake sites primarily occurred in the LAD territory. Thus, HED retention was significantly higher in the LAD territory compared with territories of the LCX and RCA in transplant recipients, while no such difference was observed in normals (Table 1).

Table 1. Results of ^{11}C-HED PET

	Heart transplant recipients			Normals (n=8)
	Group A (n=14)	Group B (n=7)	Total (n=21)	
HED retention (%/min)				
Global	5.4±1.8	4.7±1.9	5.2±1.8	11.0±0.6**
LAD	7.1±2.6	6.1±3.0	6.8±2.7	10.9±0.9**
LCX	4.5±1.8*	3.2±0.9*	4.1±1.7*	11.2±0.7**
RCA	3.8±1.0*	3.8±1.4*	3.8±1.1*	11.3±0.7**
Reinnervated area				
% of left ventricle	22.7±18.9	19.7±23.0	21.7±19.8	–

LAD, Territory of left anterior descending artery; LCX, territory of left circumflex artery; RCA, territory of right coronary artery
*P<0.01 vs LAD, **P<0.001 vs transplant recipients

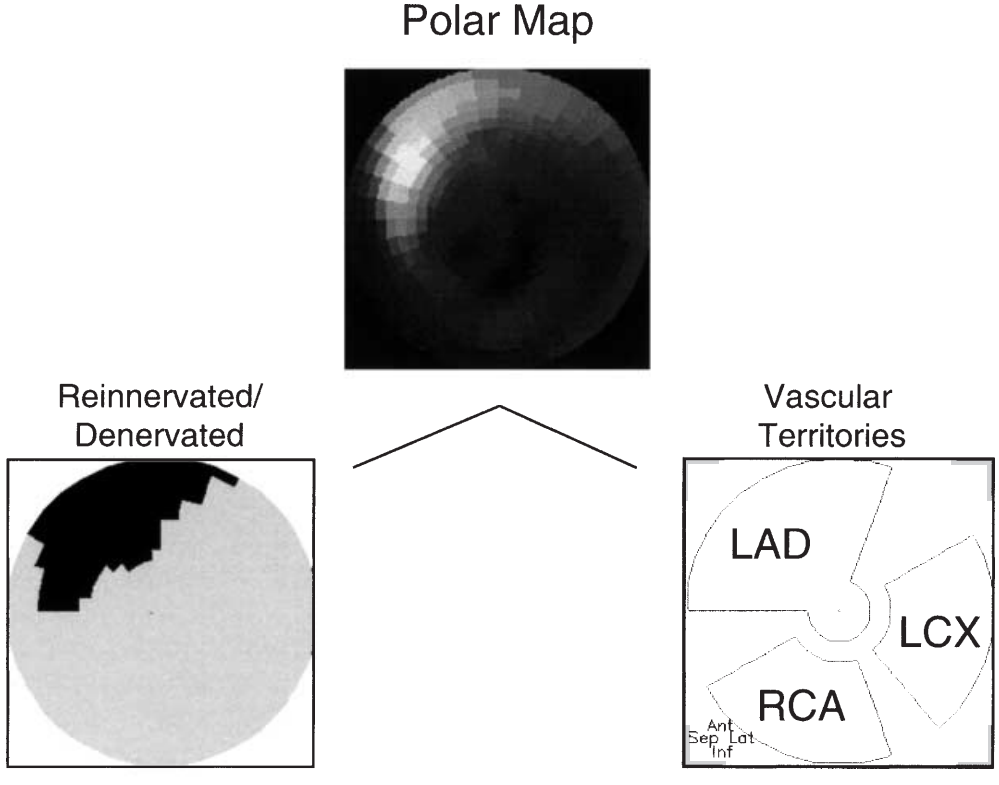

Fig. 1. Polar map of the left ventricle displaying the anterior wall at the *top*, the inferior wall at the *bottom*, the septum to the *left* and the lateral wall to the *right*. The centre of the map represents the apex, while basal areas are depicted peripherally. Shown is a map of left ventricular retention of ^{11}C-HED in a transplant recipient. Based on a threshold, regions of interest for innervated (*black*) and denervated myocardium (*grey*) are defined. Additionally, regions of interest for vascular territories of the left anterior descending (*LAD*), left circumflex artery (*LCX*) and right coronary artery (*RCA*) are applied

Table 2. Results of ^{11}C-acetate PET

	Myocardial perfusion (% of maximum)		Oxidative metabolism [k(mono) in min^{-1}]	
	Transplants (n=14)	Normals (n=11)	Transplants (n=14)	Normals (n=11)
Global	–	–	0.060±0.010	0.060±0.015
LAD	75±7	78±7	0.061±0.011	0.061±0.016
LCX	77±6	80±5	0.061±0.010	0.063±0.016
RCA	77±7	77±8	0.059±0.010	0.061±0.018

LAD, Territory of left anterior descending artery; LCX, territory of left circumflex artery; RCA, territory of right coronary artery

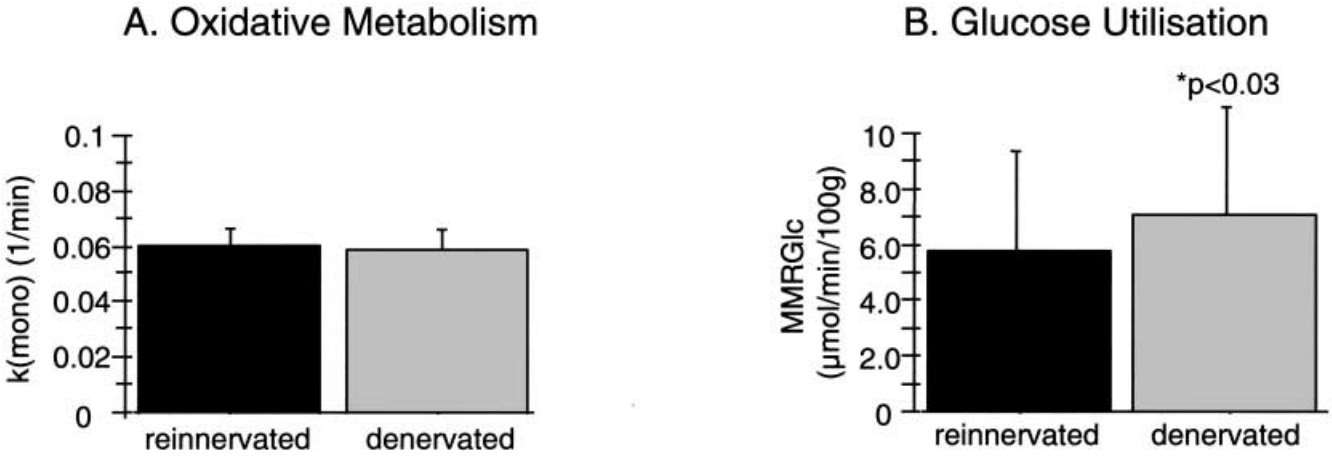

Fig. 2. Intra-individual comparison of oxidative metabolism (**A**) and glucose utilisation (**B**) in denervated and innervated areas of transplant patients. While oxidative metabolism was similar in both areas, significantly lower glucose utilisation was found in the innervated area

In transplant recipients of group A and group B, the reinnervated area and both global and regional HED retention were comparable (Table 1). Additionally, there was no difference between groups with respect to other determinants of cardiac metabolism such as plasma noradrenaline levels (1.7±1.2 pmol/l for group A vs 2.2±0.8 pmol/l for group B; P=0.37), blood glucose levels (114±19 vs 101±17 mg/dl; P=0.14) or the rate-pressure product as a measure of cardiac work (10,746± 2,177 vs 10,270±1,155; P=0.60), which were measured at the time of PET imaging.

Myocardial perfusion

Early uptake of ^{11}C-acetate as a qualitative index of regional perfusion was homogeneous in transplant patients of group A, and comparable to normals (Table 2). No perfusion defects, defined as regional uptake <50% of the maximum, were observed in any individual.

Oxidative metabolism

Global oxidative metabolism in transplant recipients of group A correlated with the rate-pressure product as a measure of cardiac work (r=0.58; P=0.03), but did not correlate with extent of reinnervated myocardium (r=–0.08; P=0.80) or global HED retention (r=0.01; P=0.97).

Regional oxidative metabolism in denervated and reinnervated myocardium of transplant recipients was comparable (0.06±0.01 vs 0.06±0.01/min; P=0.16; Fig. 2). Additionally, oxidative metabolism in three vascular territories was regionally homogeneous. A similar regional pattern was observed in normals (Table 2).

Glucose utilisation

In contrast to oxidative metabolism, MMRGlc showed high inter-individual variability. An intra-individual regional comparison between denervated and innervated myocardium in transplant recipients, however, revealed significantly higher MMRGlc in denervated myocardium (6.9±6.6 vs 6.0±6.2 µmol/min/100 g; Fig. 2).

After normalisation to the ventricular maximum, regional FDG uptake was significantly higher in the mainly denervated LCX territory compared with the partially reinnervated LAD territory of transplant patients, and showed a trend towards higher values in the denervated RCA territory compared with the LAD territory (Table 3). FDG uptake in vascular territories was signifi-

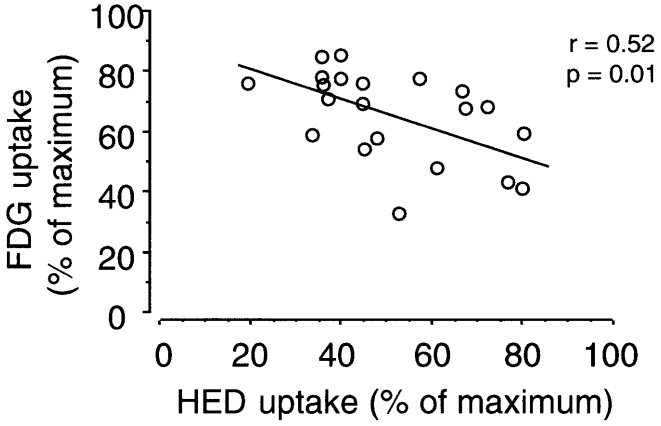

Fig. 3. Regression plot for regional uptake of HED and FDG in vascular territories of transplant patients

cantly inversely correlated with regional HED uptake (r=0.52; P=0.01; Fig. 3).

The heterogeneous regional pattern in transplant recipients was different from that in normals, in whom only a non-significant trend towards higher values in the LCX territory compared with the LAD territory could be observed (Table 3). Values for the non-LAD/LAD index were significantly higher for transplant recipients compared with controls (0.27±0.03 vs 0.07±0.03; P=0.04).

The inverse relationship between regional innervation and FDG uptake, and homogeneous oxidative metabolism despite heterogeneous innervation are illustrated in examples of transplant recipients in Fig. 4.

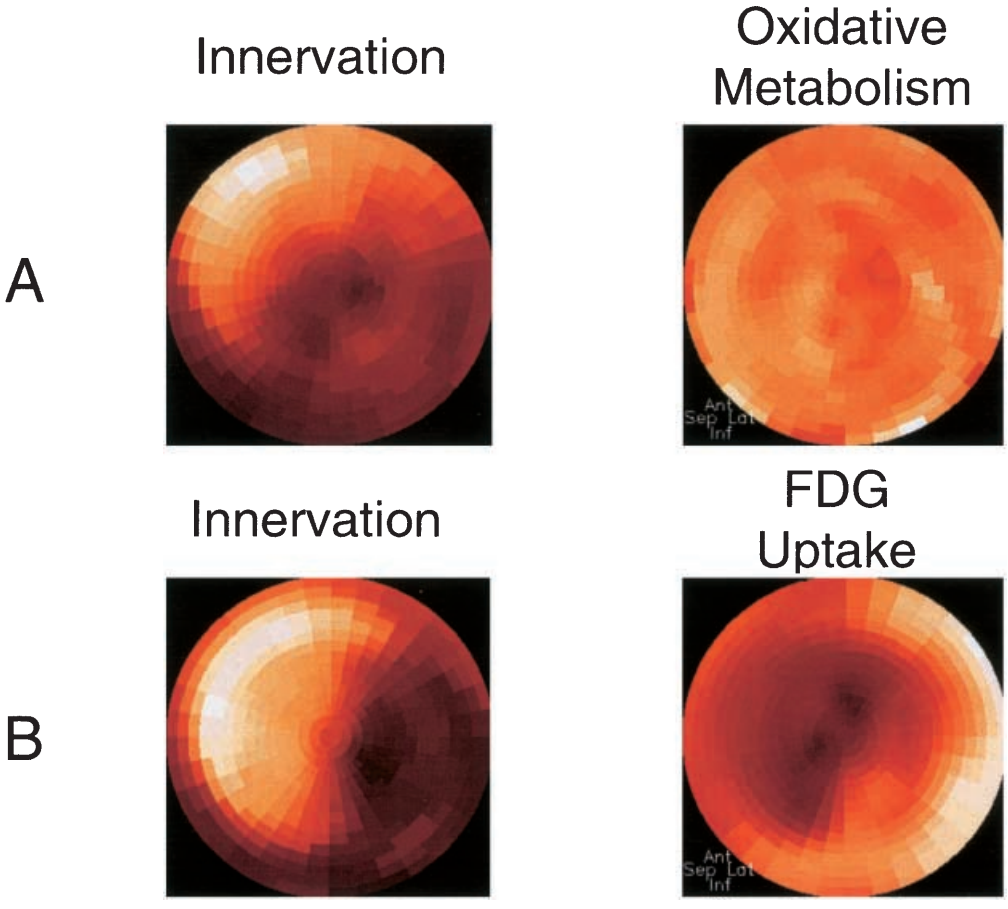

Fig. 4. Examples of polar maps of sympathetic innervation and oxidative metabolism in a transplant of group A (**A**), and of sympathetic innervation and glucose uptake in a transplant of group B (**B**). In both cases, high retention of ^{11}C-HED in the anterior and septal wall provides evidence of sympathetic reinnervation. While the clearance of ^{11}C-acetate as a measure of oxidative metabolism remains homogeneous throughout the entire left ventricle in case A, FDG uptake in case B appears to be inversely related to sympathetic innervation

Table 3. Results of ^{18}F-FDG PET

	FDG uptake (% of maximum)		MMRGlc (µmol/min/100 g)	
	Transplants (n=7)	Normals (n=7)	Transplants (n=7)	Normals (n=7)
Global	–	–	6.4±6.1	3.4±3.8
LAD	53±16*	61±10	5.9±6.0	3.3±3.7
LCX	76±6	72±12	8.0±6.7	3.9±4.4
RCA	67±10	62±11	6.8±5.9	3.2±3.4

LAD, Territory of left anterior descending artery; LCX, territory of left circumflex artery; RCA, territory of right coronary artery
*P<0.01 vs LCX and P<0.05 vs RCA

Discussion

In summary, the transplanted human heart exhibited partial sympathetic reinnervation late after transplantation. Despite regional heterogeneity of innervation, transplants showed homogeneous oxidative metabolism. PET using the glucose analogue ^{18}F-FDG, however, demonstrated higher uptake in sympathetically denervated compared with reinnervated myocardium of the same heart.

The present data suggest a direct role of cardiac sympathetic innervation in the regulation of substrate metabolism. Effects of systemic catecholamines on oxygen consumption and glucose metabolism of the myocardium have been described previously [2, 3, 4]. The effect of direct sympathetic innervation has been addressed in animal studies, where lower global rates of glucose oxidation have been reported after surgical denervation compared with measurements before denervation [7, 8]. The conclusiveness of these studies, however, was limited owing to a lack of sham-operated controls and a lack of information about the dietary state. In humans, globally increased cardiac FDG uptake has been reported previously earlier after transplantation [21]. Although sympathetic denervation was discussed as the potential mechanism, measurements to detect reinnervation or to prove denervation were not performed.

Thus, the present study for the first time provides evidence that the metabolism of human myocardium may be directly affected by the presence or absence of cardiac sympathetic efferents. Since reinnervated and denervated areas of the same heart were compared, the findings are largely independent of systemic influences such as circulating catecholamines, levels of substrates or other hormones, and cardiac workload.

Consistent with previous studies, hearts of healthy normals showed regionally homogeneous innervation [22] and oxidative metabolism [23]. Metabolic rates of glucose in normals have previously been shown to be inter-individually variable and regionally heterogeneous, with a gradient from the anterior to the posterolateral wall [23, 24]. This is confirmed by the present data, where a high inter-individual variability of FDG uptake and a slight regional heterogeneity were found in normals. In transplants, however, the non-LAD/LAD index for MMRGlc was significantly higher compared with normals. Additionally, regional FDG uptake was inversely correlated with HED uptake, suggesting that the observed intra-individual heterogeneity is abnormal and associated with regional differences in catecholamine uptake sites. In addition to analysis of vascular territories, an approach with regions of interest directly encompassing reinnervated and denervated areas in each transplant recipient was applied. As the localisation and extent of reinnervation vary [10], this approach is expected to be more precise, and further confirms significantly higher FDG uptake in denervated areas.

The exact mechanism for the observed effect of sympathetic innervation on substrate metabolism cannot be determined from this clinical study. Several factors, however, have to be taken into consideration:

First, an inverse relationship between utilisation of fatty acids and glucose as two major substrates of cardiac energy metabolism has been demonstrated [25]. Denervation may cause a shift in preferential substrate utilisation. Speculatively, higher uptake of glucose in denervated myocardium may be accompanied by or secondary to reduced rates of oxidation of free fatty acids. Innervated areas may preferentially use fatty acids, while denervation may result in reduced capability to utilise fatty acids for energy production. This hypothesis is consistent with previous studies demonstrating reduced fatty acid oxidation after adrenergic deactivation by beta-receptor blockade in failing hearts [26].

Secondly, supersensitivity towards circulating catecholamines has been described previously for denervated myocardium [27], and may contribute to increased utilisation of glucose. Denervation supersensitivity, however, may occur acutely, but is unlikely in a chronic model of denervation [28].

Thirdly, variations of myocardial blood flow may affect the level of regional glucose utilisation. Ischaemia and hypoperfusion are strong determinants of the contribution of glucose as a substrate for cardiac energy production [29]. Regional flow abnormalities caused by transplant vasculopathy not detected by coronary angiography, or by myocardial insults due to previous rejection episodes, may have contributed to heterogeneity of glucose uptake in the present study. However, the likelihood of such insults is similar for all myocardial territories, and regionally homogeneous perfusion was demonstrated in the present study using an uptake index for ^{11}C-acetate. Di Carli et al. recently demonstrated that regulation of myocardial blood flow is impaired in sympathetically denervated myocardium [22]. However, denervation influenced blood flow under stress conditions only, while flow at rest remained unaffected [22]. It therefore seems unlikely that the observed metabolic changes at rest in the present study are secondary to an effect of denervation on regional blood flow.

Finally, for interpretation of MMRGlc derived from FDG imaging, it needs to be considered that the lumped constant, a factor introduced to correct for lower affinity of glucose transport and phosphorylation to FDG, has been shown to vary with metabolic conditions [30]. Regional differences in this constant are difficult to assess non-invasively in vivo. Thus, consistent with previous data [14], a fixed value was used in the present study. Theoretically, an effect of sympathetic innervation on the lumped constant could contribute to the observed regional differences in MMRGlc between innervated and denervated myocardium. It is, however, very unlikely that variations in the lumped constant are the only explanation for the results, because such variations have previ-

ously been described mainly under conditions which also influence true glucose utilisation. An effect of innervation on the lumped constant would only confirm an influence of innervation on regional cardiac substrate metabolism.

Clearance kinetics of ^{11}C-acetate, a validated measure of overall oxidative metabolism, remained homogeneous throughout the transplanted heart in the present study. The lack of difference between reinnervated and denervated myocardium in this regard suggests that production of high-energy phosphates through the tricarboxylic acid cycle and subsequent oxidative phosphorylation as the final common pathway of all myocardial substrates are maintained at a constant level despite chronic denervation. These results are consistent with a recent animal study, where normal tissue levels of high-energy phosphates and normal mitochondrial oxidative function were observed in denervated canine hearts [31]. Previous studies using ^{11}C-acetate demonstrated that oxidative metabolism is independent of the underlying pattern of substrate utilisation and is mainly determined by cardiac work [13]. Thus, efferent sympathetic denervation seems to influence substrate utilisation without a measurable effect on overall oxidative metabolism.

In summary, the present data support a role of efferent sympathetic signals for modulation of glucose uptake of the heart. This effect may have clinical implications: The lack of sympathetic efferent signals due to denervation early after heart transplantation may result in reduced capability to adapt substrate utilisation to changing environmental conditions. Furthermore, myocardial ischaemia and heart failure have been shown to profoundly influence sympathetic innervation [32, 33]. Impaired presynaptic sympathetic integrity may contribute to metabolic abnormalities in coronary artery disease and in the failing heart. Further studies may be warranted in the future to investigate potential implications of metabolic effects of cardiac innervation in clinical settings.

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